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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,913	02/17/2005	Milan Dittrich	J187-027 US	3010

21706 7590 07/18/2008

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EXAMINER	
SASAN, ARADHANA	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
07/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,913	DITTRICH ET AL.	
	Examiner	Art Unit	
	ARADHANA SASAN	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The remarks and amendments filed on 5/12/08 are acknowledged.

2. Claims 12, 13 and 17 were amended.

3. Claims 12-17 are included in the prosecution.

Response to Arguments

Claim Objections

4. In light of Applicant's amendments to claims 12, 13 and 17, the claim objections of 2/21/08 are withdrawn.

Rejection of claim 13 under 35 USC § 103(a)

5. In light of Applicant's amendment to claim 13, the rejection of 2/21/08 is withdrawn.

Rejection of claim 12 under 35 USC § 103(a)

6. Applicant's arguments, see Page 4, filed 5/12/08, with respect to the rejection of claim 12 under 35 USC § 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Chen et al. (J. Microencapsulation, 1999, Vol. 16, No. 5, 551-563) have been fully considered but are not persuasive.

Applicant argues that the present invention is a plastic, monolithic, non-particulate system and that the composition of claim 12 can be prepared merely by heating the active matter in the presence of the carrier. Applicant argues that both Hampl and Chen are structurally very different from the present invention. Applicant

argues that both Hampl and Chen have a different release mechanism than that of the present invention.

This is not found persuasive because the broadest definition of "monolithic" (from Merriam-Webster's Collegiate Dictionary, Tenth edition, 2001, page 751) is: consisting of or constituting a single unit. The microspheres of Hampl are single units. Moreover, the microspheres of Hampl are administered subcutaneously and one with ordinary skill in the art would know that subcutaneous administration will intrinsically encompass the microspheres in a solution and not just the administration of the microspheres alone. Moreover, Hampl is combined with Chen, which also teaches an injectable composition (Abstract). Therefore, the monolithic limitation of amended claim 12 is rendered obvious by the teachings of Hampl and Chen.

Therefore, the rejection of 2/21/08 is maintained.

Rejection of claims 13-17 under 35 USC § 103(a)

7. Applicant's arguments, see Page 6, filed 5/12/08, with respect to the rejection of claim 12 under 35 USC § 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Chen et al. (J. Microencapsulation, 1999, Vol. 16, No. 5, 551-563) and further in view of Berggren et al. (US 5,783,205) have been fully considered but are not persuasive.

Applicant argues that the instant preparation method produces different quality final products than that of the preparation method in Berggren. Applicant argues that in the polycondensation reaction of the present invention both the distribution and arrangement can be controlled by terminating the reaction when desired parameters are reached. Applicant argues that when precipitating, the matrix materials of Berggren are

contaminated with the used solvents, the elimination of which is not possible. Applicant argues that as distinct from the biodegradable oligoesters of the present invention, the matrix materials of Berggren prepared by the cycle-opening polymerisation in the presence of the polyhydric alcohols exhibit a low branching rate when having a low molecular weight. Applicant argues that the low branching rate of the oligomers used in Berggren the resulting oligoester material shows lower content of end hydroxyl groups, which influence the kinetics of the release of the active matter. Applicant argues that no such effect occurs with the biodegradable oligoesters of the present invention.

This is not found persuasive because Applicant is arguing against Berggren individually. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In this case, Berggren is used as a supporting reference to provide the teaching of a liquid biocompatible plasticizer that can be used in a matrix comprising a bioerodible polymer (Col. 4, lines 48-57).

Applicant argues that the composition of present claims 12 through 17 comprised as a matrix carrier is structurally (and with respect to the presence of accompanying substances) different from the carrier material disclosed in Berggren. Applicant argues that a person skilled in the art would not have thought to use the teaching of Berggren in a composition designed primarily for intratissue administration.

This is not found persuasive because the limitations of the carrier material recited in instant claim 12 are met by the oligoesters taught by Hampl (Abstract) and by the antitumor active ingredient taught by Chen (Abstract).

Therefore, the rejection of 2/21/08 is maintained.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As amended, instant claim 12 recites the limitation "monolithic" with respect to the biodegradable antitumor composition.

After carefully examining the instant disclosure, the examiner respectfully submits that support for this amendment is lacking and the addition of said limitation is new matter. Although the term "monolithic" is disclosed in the instant specification, it is in the context of monolithic type implantable systems in the prior art (Instant Specification, Page 1). This limitation of the biodegradable, antitumor composition was not set forth and is considered new matter.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of Chen et al. (J. Microencapsulation, 1999, Vol. 16, No. 5, 551-563).

The claimed invention is a biodegradable, monolithic antitumor composition with prolonged release of an antitumor agent for administration into tissues, comprising: at least one antitumor agent and a carrier, consisting of biodegradable oligoester, having the numeric mean relative molecular mass M_n from 650 to 7,500, the mass mean relative molecular mass M_w from 800 to 10,000 and the glass transition temperature T_g from -35 to 45ºC, and which is prepared by polycondensation reaction of polyhydric alcohol containing at least 3 hydroxy groups with at least one aliphatic α- hydroxy acid in the molar ratio of polyhydric alcohol to aliphatic a-hydroxy acid being from 0.5:99.5 to 12:88, wherein the essential molecule of biodegradable oligoester is a polyhydric alcohol, to the hydroxy groups of which chains created from several molecules of at least one aliphatic a-hydroxy acid are bound by ester bonds, and in that it is in the form of homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion.

Hampl teaches oligoesters, specifically, a terpolymer (GA-M-DLLA) of DL-lactic acid (LA), glycolic acid (GA) and mannitol (MA), a copolymer DL-lactic acid and mannitol (M-DLLA) and lactide-glycolide copolymers (DL-PLGA) (Abstract). The GA-M-DLLA was prepared by the polycondensation reaction (Page 108, 2.2 Preparation of oligoesters) of LA (45.05 mol), GA (45.06 mol) and MA (0.9 mol) and has a T_g of 20ºC, M_n of 2.20Kda and M_W of 3.95 kDa (Page 108, Table 1). Bovine serum albumin (BSA) was the active ingredient entrapped in microspheres prepared with the terpolymer of

GA-M-DLLA which depicted prolonged release of BSA over 15 weeks (Abstract and Figures 4 and 5). The microspheres were administered subcutaneously to mice (Page 109, 2.6 Biological Experiment).

Hampl does not expressly teach the incorporation of an antitumor active ingredient or compound in the composition comprising a terpolymer prepared by a polycondensation reaction.

Chen teaches injectable carboplatin-loaded poly (D,L-lactic-co-glycolic) acid copolymer (PLGA) microspheres for the intracerebral treatment of malignant glioma (Abstract). "PLGA was selected as the matrix because of its well-established biocompatibility and biodegradation in rat brains ... (and) carboplatin is a potent anticancer agent" (Page 552). Chen teaches that the advantage of incorporating "carboplatin into PLGA and then direct intracerebral delivery to the brain tumour regions can minimize these side effects and improve the efficacy" (Page 552). The PLGA microspheres were prepared by the emulsion/solvent evaporation method (Page 553). Figure 1 shows the prolonged release of carboplatin from the PLGA microspheres (Page 557).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a prolonged release, biodegradable composition with an active ingredient and a terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction), as suggested by Hampl, combine it with a biodegradable anti-tumor composition comprising PLGA, as suggested by Chen, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Chen teaches that the advantage of incorporating "carboplatin into PLGA and then direct intracerebral delivery to the brain tumour regions can minimize ... side effects and improve the efficacy" (Page 552). One with ordinary skill in the art would substitute the BSA used by Hampl with an active ingredient with anti-tumor properties (such as the carboplatin used by Chen) and use it in the prolonged release, biodegradable composition comprising oligoesters, with a reasonable expectation of success regarding long term release of the active ingredient.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Regarding instant claim 12, the biodegradable composition with prolonged release would have been obvious over the biodegradable composition with prolonged release taught by Hampl (Abstract and Page 108, Table 1). The limitation of the antitumor composition and the antitumor agent would have been obvious over the antitumor composition comprising carboplatin taught by Chen (Abstract). The limitation of the "antitumor agent for administration into tissues" would have been obvious over the subcutaneous administration of the composition to mice, as taught by Hampl (Page 109, 2.6 Biological Experiment) in view of the antitumor composition comprising carboplatin taught by Chen (Abstract). The limitation of the biodegradable oligoester

would have been obvious over the terpolymer (GA-M-DLLA) taught by Hampl (Abstract). The limitation of the M_n from 650 to 7,500, the M_w from 800 to 10,000, and the T_g from -35 to 45ºC, would have been obvious over the M_n of 2.20Kda, M_W of 3.95 kDa, and T_g of 20ºC, as taught by Hampl (Page 108, Table 1). The limitation of the polycondensation reaction would have been obvious over the GA-M-DLLA that was prepared by polycondensation reaction, as taught by Hampl (Page 108, 2.2 Preparation of oligoesters). The limitation of the polyhydric alcohol containing at least 3 hydroxy groups would have been obvious over the mannitol in the oligoester taught by Hampl (Abstract). The limitation of the aliphatic α-hydroxy acid would have been obvious over the DL-lactic acid in the oligoester taught by Hampl (Abstract). The molar ratio of the polyhydric alcohol to aliphatic α-hydroxy acid would have been obvious over the ratio of mannitol to DL-lactic acid (0.9:45.05) taught by Hampl (Page 108, Table 1). The limitation of the form of the composition as a homogenous one-phase solution, micellar colloid system, one-phase or two-phase gel, suspension, paste or emulsion would have been obvious over the subcutaneous administration of the composition taught by Hampl (Page 109, 2.6 Biological Experiment) and over the injectable composition taught by Chen (Abstract). One with ordinary skill in the art would formulate the composition for subcutaneous administration or for injection by preparing a homogenous solution or emulsion prior to the administration. This formulation would include modifying the viscosity of the composition in order to optimize delivery of the composition.

12. Claims 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hampl et al. (International Journal of Pharmaceutics 144 (1996) 107-114) in view of

Chen et al. (J. Microencapsulation, 1999, Vol. 16, No. 5, 551-563) and further in view of Berggren et al. (US 5,783,205).

The teachings of Hampl and Chen are stated above.

Hampl and Chen do not expressly teach a composition further comprising a liquid biocompatible plasticizer.

Berggren teaches a drug delivery device (injection) comprising an antibiotic drug and a matrix comprising a bioerodible polymer "selected from polylactic acid, polyglycolic acid, copolymers of lactic acid and glycolic acid, polylactide-co-glycerate, polyglycolide-co-glycerate and poly(orthoesters), or a bioerodible oligomer selected from oligomers of hydroxycarbonic acids and oligomers of glycolic acid and/or lactic acid and their derivatives with alcohols and/or carbonic acids" (Col. 4, lines 48-57). "The delivery device of the invention may also optionally include an amount of a plasticizer to alter the viscosity of the matrix material so that it falls within the range required by the present invention ... Suitable biocompatible plasticizers include ... triethyl citrate, acetyl triethyl citrate ... propylene oxide ... when a plasticizer is included in the matrix material, it is generally present in an amount of from about 5 to about 30 wt %, preferably from about 7 to about 20 wt %" (Col. 9, lines 45-67).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a prolonged release, biodegradable composition with an active ingredient and a terpolymer (GA-M-DLLA - that is prepared by a polycondensation reaction), as suggested by Hampl, combine it with a biodegradable anti-tumor composition comprising PLGA, as suggested by Chen, and further combine it

with the use of a plasticizer in a biodegradable and injectable composition, as taught by Berggren, and produce the instant invention.

One of ordinary skill in the art would have been motivated to do this because Berggren teaches that the use of a plasticizer depends on the matrix material used, for example for keeping the material from becoming too hard and brittle (Col. 9, lines 48-53).

Regarding instant claims 13-14, the limitations of the one liquid biocompatible plasticizer and the plasticizer soluble in the carrier would have been obvious over the plasticizer used in the matrix material to alter the viscosity, as taught by Berggren (Col. 9, lines 45-67). One with ordinary skill in the art would know that in order to successfully alter the viscosity of the matrix material, the plasticizer used would have to be soluble in the matrix material. The limitation of the weight ratio of the plasticizer to oligoester (claim 13) would have been obvious over the ratio of triethyl citrate to PLGA, which ranges from 1:4.33 to 1:9, as shown in examples 2-5 by Berggren (Col. 13, Table B, lines 55-63).

Regarding instant claim 15, the limitation of an agent influencing the kinetics of the release of the antitumor agent would have been obvious over the "drug release-rate regulating agents" taught by Berggren (Col. 10, lines 1-2).

Regarding instant claim 16, the limitation of a stabilizer of the antitumor agent or carrier would have been obvious over the stabilizers taught by Berggren (Col. 10, lines 1-3).

Regarding instant claim 17, the limitation of heating an antitumor agent, a carrier, optionally a plasticizer, an agent influencing the kinetics of the release of the antitumor

agent, and a stabilizer of the antitumor agent or a stabilizer, would have been obvious over the composition taught by Hampl, in view of the antitumor agent taught by Chen, and further in view of the teaching by Berggren that the "matrix material is heated to soften the material to a point where it becomes flowable and can be delivered at a physiologically compatible elevated temperature into a biological pocket" (Col. 4, lines 14-17). One with ordinary skill in the art would heat the mixture depending on the constituents (polymer matrix, active ingredient) and depending on the administration site. The recited temperature range of 35 to 75ºC would have been an obvious variant during the process of routine experimentation, unless there is evidence of criticality or unexpected results.

Conclusion

13. No claims are allowed.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aradhana Sasan whose telephone number is (571) 272-9022. The examiner can normally be reached Monday to Thursday from 6:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Aradhana Sasan/
Examiner, Art Unit 1615

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